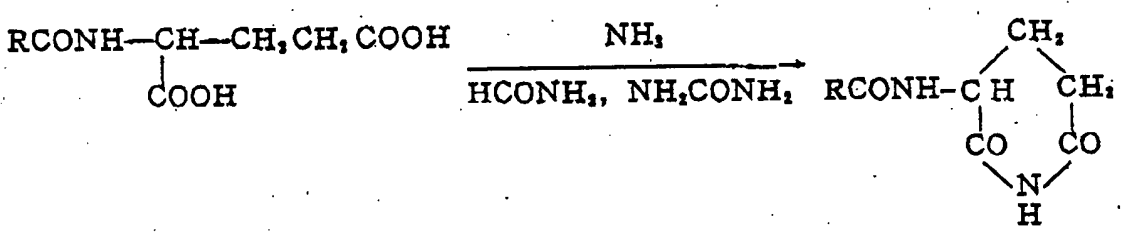
Kokoku (Jpn. Examined Patent Publication) No. 36-14610
Title of the Invention: Method for Preparing Acyl Derivative of α–aminoglutarimide
Publication Date: August 29, 1961
Application No. 32-12745
Filing Date: May 24, 1957
Applicant: Dainippon Pharmaceutical Co., Ltd.

Detailed Description of the Invention

The present invention relates to a method for the preparation of an acyl derivative of an α– acylaminoglutarimide. The method of the invention is shown by the following reaction formula:



(wherein RCO represents a saturated or unsaturated, aliphatic or aromatic acyl group)

The reaction described in the above formula is carried out by reacting, under heat, a N-acylglutamic acid with ammonia, formamide or urea.

The compound of the present invention is an antivirus compound and is useful as a remedy for diseases caused by pathogenic viruses.

For instance, the remedial effects against Japanese encephalitis are shown in the table below.

The test method is as follows:

as for the virus, *Japanese encephalitis virus Nakayama strain* was used and as for mice, inbred D. M. K. mice, weighing about 10 g or so, 3 weeks postnatal, were used;

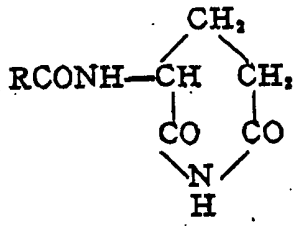
brains of mice at the fastigium period were emulsified using Lush's solution to which 10 % blood serum was added;

the mice were inoculated by the intra-nasal routes with three drops of a solution having a prescribed concentration of virus under etherization so as to be

infected with the viruses;

72 hours thereafter each medicine to be tested was injected into the mice; and the resultant LD_{50} values were calculated after 14 days' observation.

N-lauroylglutamic acid was used as a control medicine in the test. Any of the compounds according to the present invention produces remedial effects superior to those of N-lauroylglutamic acid when used as a raw material.



Cpd. R	Dose mg/kg	Density of Virus Inoculation (internasal infection)					LD_{50}
		$10^{-2.4}$	$10^{-2.8}$	$10^{-3.16}$	$10^{-3.32}$	$10^{-3.64}$	
$CH_3(CH_2)_2$-	100	1/14	8/14	12/14	12/14	13/14	$10^{-2.92}$
CH_3 / CH_3 > CH-	100	2/14	8/14	12/14	12/14	12/14	$10^{-2.92}$
$CH_3(CH_2)_3$-	100	2/14	7/14	12/14	13/14	13/14	$10^{-2.91}$
$CH_3(CH_2)_4$-	100	3/14	8/15	10/14	12/14	14/14	$10^{-2.90}$
$CH_3(CH_2)_5$-	100	1/14	8/14	12/14	12/14	12/14	$10^{-2.92}$
$CH_3(CH_2)_6$-	100	3/15	8/14	12/14	12/14	14/14	$10^{-2.88}$
$CH_3(CH_2)_7$-	100	3/14	8/15	11/15	12/15	13/14	$10^{-2.86}$
$CH_3(CH_2)_8$-	75	3/14	8/14	12/14	12/15	13/14	$10^{-2.84}$
$CH_3(CH_2)_9$-	75	3/15	8/14	11/14	12/15	14/14	$10^{-2.88}$
CH_2=$CH(CH_2)_8$-	75	3/14	7/14	11/14	13/15	13/14	$10^{-2.84}$
$CH_3(CH_2)_{10}$-	75	3/14	8/14	12/14	12/14	13/14	$10^{-2.82}$
$CH_3(CH_2)_{12}$-	75	3/14	8/15	12/15	12/14	13/14	$10^{-2.86}$
$CH_3(CH_2)_{14}$-	75	2/14	8/14	12/14	12/14	13/14	$10^{-2.92}$
C_6H_5 -	100	1/15	8/14	11/15	12/15	13/15	$10^{-3.11}$
Control Medicine N-lauroylglutamic Acid	100	3/15	8/15	10/14	12/14	12/14	$10^{-2.96}$
Control	-	0/15	3/15	8/15	11/15	12/15	$10^{-3.20}$

(In the above table, the denominator represents the number of mice used and the numerator represents the number of mice free of crisis)

Next, the invention is illustrated using the examples according to the present invention.

Example 1

A method for the preparation of an α– benzoylaminoglutarimide

After 2g of an N– benzoylaminoglutamic acid is dissolved into excessive amount of ammonia water, the solution is evaporated and dried under reduced pressure and the residue is heated at 170-190°C for about 30 minutes. Then, it is washed with water and is recrystallized from alcohol to give the target compound, as crystals having a melting point of 213-215°C (decomposition).

The yield is 0.8 g.

Analysis: $C_{12}H_{12}O_2N_2$

Calculated Value	C 62.06 %	H 5.20 %	N 12.05%
Experimental Value	C 62.18 %	H 5.02 %	N 11.86%

Example 2

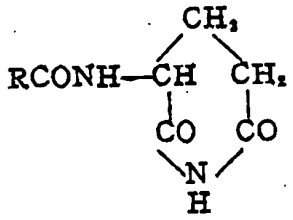
A method for the preparation of α– lauroylglutarimide

0.4g of formamide is added to 1.5g of an N– benzoylaminoglutamic acid and the solution is heated at 170-190°C for about 5 hours. The residue is washed with water and the insoluble substances are recrystallized from a mixture of alcohol and petroleum benzin to give the target compound, as crystals having melting point of 150°C. The yield is 0.4 g.

Analysis: $C_{17}H_{30}O_2N_2$

Calculated Value	C 65.8 %	H 9.75 %	N 9.03 %
Experimental Value	C 65.55 %	H 9.27 %	N 9.16 %

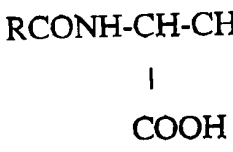
As prepared in the same manner as in Example 1 or 2, a compound shown in the following table can be obtained.



R	Melting Point °C	Molecular Formula	Analytic Value (%)	
			Calculated Value	Experimental Value
$CH_3(CH_2)_2$-	168-170	$C_9H_{14}O_3N_2$	C 54.54 H 7.12 N 14.13	C 54.81 H 7.28 N 14.22
CH_3 CH_3 > CH -	209-211	$C_9H_{14}O_3N_2$	C 54.54 H 7.12 N 14.13	C 54.59 H 7.35 N 14.23
$CH_3(CH_2)_3$-	151-152	$C_{10}H_{16}O_3N_2$	C 56.59 H 7.60 N 13.20	C 56.51 H 7.68 N 13.14
$CH_3(CH_2)_4$-	146-147.5	$C_{11}H_{18}O_3N_2$	C 58.39 H 8.02 N 12.38	C 58.49 H 8.12 N 12.24
$CH_3(CH_2)_5$-	147-148	$C_{12}H_{20}O_3N_2$	C 59.98 H 8.39 N 11.66	C 60.09 H 8.57 N 11.67
$CH_3(CH_2)_6$-	148-149	$C_{13}H_{22}O_3N_2$	C 61.39 H 8.72 N 11.02	C 61.06 H 8.68 N 11.11
$CH_3(CH_2)_7$-	147-148	$C_{14}H_{24}O_3N_2$	C 62.66 H 9.02 N 10.44	C 62.93 H 9.18 N 10.43
$CH_3(CH_2)_8$-	148-150	$C_{15}H_{26}O_3N_2$	C 63.80 H 9.28 N 9.92	C 63.73 H 9.17 N 9.94
$CH_3(CH_2)_9$-	148-149	$C_{16}H_{28}O_3N_2$	C 64.84 H 9.52 N 9.45	C 65.10 H 9.68 N 9.49
CH_2=$CH(CH_2)_8$-	138-139	$C_{16}H_{26}O_3N_2$	C 65.28 H 8.90 N 9.52	C 64.97 H 9.05 N 9.40
$CH_3(CH_2)_{12}$-	147-148	$C_{19}H_{34}O_3N_2$	C 67.42 H 10.13 N 8.28	C 67.44 H 10.25 N 8.31
$CH_3(CH_2)_{14}$-	143-144	$C_{21}H_{38}O_3N_2$	C 68.81 H 10.45 N 7.64	C 69.09 H 10.52 N 7.59

CLAIM:

A method for the preparation of an α– acylaminoglutarimide derivative, comprising reacting under heat an N-acylglutamic acid with ammonia, formamide or urea, wherein said N-acylglutamic acid contains a compound represented by the general formula:



(wherein RCO represents a saturated or unsaturated, aliphatic or aromatic acyl group, exclusive of acetyl groups)

16 B 65
(16 E 431)
(30 B 1)

特許庁

特許出願公告

特許公報

昭36—14610

公告 昭 36.8.29　出願 昭 32.5.24　特願 昭 32—12745

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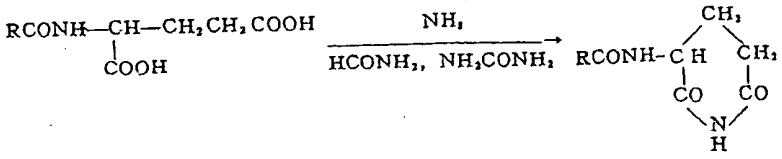
(全2頁)

α—アミノグルタルイミドのアシル誘導体の製造法

発明の詳細なる説明

本発明はα—アミノグルタルイミドのアシル誘導体の製法に係る。

次に本発明の方法を化学反応式で示す。



(式中、RCOは飽和又は不飽和の脂肪族、芳香族のアシル基を示す)

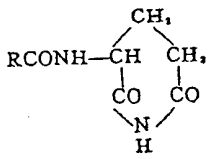
前式に於て示される反応は、N—アシルグルタミン酸をアンモニア、ホルムアミド又は尿素と加熱反応せしめる事によつて進められる。

本発明の方法によつて得られる化合物は抗ビールス性を有し、病原性ビールスに基因する諸疾患の治療薬として利用される。

例えば、日本脳炎に対する治療効果は次表に示す通りである。

試験方法は、ビールスとしては日本脳炎中山株ビールスを用い、マウスには純系D. M. K. 系マウスの生後3週目、体重約10 g前後のものを用いる。発症極期のマウスの脳を10%血清加ルツシユ氏液で乳剤とし、これをエーテル麻酔下に所要濃度のビールス液を3滴経鼻感染せしめ、その72時間後各被検薬物を静注し、14日間観察してLD_{50}を計算する方法である。

尚、薬物対照としてN—ラウロイルグルタミン酸を用いたが、本発明方法の化合物はいずれも原料としてのN—ラウロイルグルタミン酸よりも優れた治療効果を有する。



(表中、分母は使用マウス数、分子は非発症マウス数を示す。)

化合物 R	用量 mg/kg	ビールス接種濃度(経鼻感染) $10^{-2.4}$	$10^{-2.8}$	$10^{-3.16}$	$10^{-3.52}$	$10^{-3.64}$	LD_{50}
$CH_3(CH_2)_2-$	100	1/14	8/14	12/14	12/14	13/14	$10^{-3.02}$
$(CH_3)_2CH-$	100	2/14	8/14	12/14	12/14	12/14	$10^{-3.02}$
$CH_3(CH_2)_3-$	100	2/14	7/14	12/14	13/14	13/14	$10^{-3.01}$
$CH_3(CH_2)_4-$	100	3/14	8/15	10/14	12/14	14/14	$10^{-2.99}$
$CH_3(CH_2)_5-$	100	1/14	8/14	12/14	12/14	12/14	$10^{-3.02}$
$CH_3(CH_2)_6-$	100	3/15	8/14	12/14	12/14	14/14	$10^{-3.00}$
$CH_3(CH_2)_7-$	100	3/14	8/15	11/15	12/15	13/14	$10^{-2.96}$
$CH_3(CH_2)_8-$	75	3/14	8/14	12/14	12/15	13/14	$10^{-2.94}$
$CH_3(CH_2)_9-$	75	3/15	8/14	11/14	12/15	14/14	$10^{-2.98}$
$CH_2=CH(CH_2)_8-$	75	3/14	7/14	11/14	13/15	13/14	$10^{-2.94}$
$CH_3(CH_2)_{10}-$	75	3/14	8/14	12/14	12/14	13/14	$10^{-2.93}$
$CH_3(CH_2)_{11}-$	75	3/14	8/15	12/15	12/14	13/14	$10^{-2.96}$
$CH_3(CH_2)_{14}-$	75	2/14	8/14	12/14	12/14	13/14	$10^{-2.93}$
C_6H_5-	100	1/15	8/14	11/15	12/15	13/15	$10^{-2.11}$
対照薬物 N—ラウロイルグルタミン酸	100	3/15	8/15	10/14	12/14	12/14	$10^{-2.90}$
対照	—	0/15	3/15	8/15	11/15	12/15	$10^{-2.28}$

次に本発明の実施例をあげて説明する。

実施例　1

α—ベンゾイルアミノグルタルイミドの製法

N—ベンゾイルグルタミン酸2gを過剰のアンモニア水に溶解後減圧下に蒸発乾固し、残渣を170～190℃で約30分間加熱する。次にこれを水洗し、アルコールより再結晶すれば目的物は融点213～215℃（分解）の結晶として得られる。

収量0.8g。

分析：$C_{11}H_{11}O_2N_2$

計算値	C62.06%	H5.20%	N12.05%
実験値	C62.18%	H5.02%	N11.86%

実施例　2

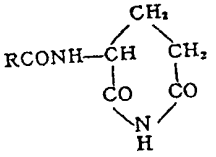
α—ラウロイルアミノグルタルイミドの製法

N—ラウロイルグルタミン酸1.5gにホルムアミド0.4gを加え、170～190℃で約5時間加熱後水洗し、不溶物をアルコール—石油ベンジンの混液より再結晶すれば目的物は融点150℃を示す結晶として得られる。収量0.4g。

分析：$C_{17}H_{30}O_2N_2$

計算値	C65.8%	H9.75%	N9.03%
実験値	C65.55%	H9.27%	N9.16%

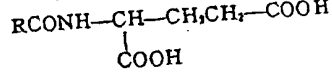
前記実施例1又は2の方法と全く同様に処理して次表に示す化合物が得られる。



R	融点℃	分子式	分析値（%） 計算値	実験値
$CH_3(CH_2)_3-$	168～170	$C_9H_{14}O_2N_2$	C54.54 H 7.12 N14.13	C54.81 H 7.28 N14.22
CH_3 CH_3>CH-	209～211	$C_9H_{14}O_2N_2$	C54.54 H 7.12 N14.13	C54.59 H 7.35 N14.23
$CH_3(CH_2)_4-$	151～152	$C_{10}H_{16}O_2N_2$	C56.59 H 7.60 N13.20	C56.51 H 7.68 N13.14
$CH_3(CH_2)_4-$	146～147.5	$C_{11}H_{18}O_2N_2$	C58.39 H 8.02 N12.38	C58.49 H 8.12 N12.24
$CH_3(CH_2)_5-$	147～148	$C_{11}H_{20}O_2N_2$	C59.98 H 8.39 N11.66	C60.09 H 8.57 N11.67
$CH_3(CH_2)_6-$	148～149	$C_{12}H_{22}O_2N_2$	C61.39 H 8.72 N11.02	C61.06 H 8.68 N11.11
$CH_3(CH_2)_7-$	147～148	$C_{13}H_{24}O_2N_2$	C62.66 H 9.02 N10.44	C62.93 H 9.18 N10.43
$CH_3(CH_2)_8-$	148～150	$C_{14}H_{26}O_2N_2$	C63.80 H 9.28 N 9.92	C63.73 H 9.17 N 9.94
$CH_3(CH_2)_9-$	148～149	$C_{15}H_{28}O_2N_2$	C64.84 H 9.52 N 9.45	C65.10 H 9.68 N 9.49
$CH_2=CH$ $(CH_2)_8-$	138～139	$C_{15}H_{26}O_2N_2$	C65.28 H 8.90 N 9.52	C64.97 H 9.05 N 9.40
$CH_3(CH_2)_{12}-$	147～148	$C_{19}H_{34}O_2N_2$	C67.42 H10.13 N 8.28	C67.44 H10.25 N 8.31
$CH_3(CH_2)_{14}-$	143～144	$C_{21}H_{38}O_2N_2$	C68.81 H10.45 N 7.64	C69.09 H10.52 N 7.59

特許請求の範囲

一般式



（式中RCOは飽和又は不飽和の脂肪族或は芳香族のアシル基を示す。但しアセチル基を除く。）

を有するN—アシルグルタミン酸をアンモニア，ホルムアミド又は尿素と加熱反応せしめる事を特徴とするα—アシルアミノグルタルイミド誘導体の製法。